infoaging guides

BIOLOGY OF AGING

DNA Damage and Repair

An introduction to aging science brought to you by the American Federation for Aging Research

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DNA BASICS

DNA stands for deoxyribonucleic acid. The nucleus of each human cell contains forty-six structures called chromosomes that together "package" all our genetic information or genes. This information is coded by a series of four bases: adenine, guanine, cytosine, and thymine. These are linked together in a specific sequence or code. In addition, each strand of code has a complementary strand in which the bases are paired: adenine pairs with thymine and cytosine pairs with guanine. The base pairs are like rungs in long, twisting, zipper-like genetic ladders. These base pairs create the sequences, or instructions needed to form our bodies.

Genes are portions of this genetic material critical to growth and reproduction. They also have important day-to-day functions. For example, genes carry the instructions for making proteins, enzymes, and others substances that in turn carry out many cellular processes, such as energy generation and hormone creation. All of our cells, except sperm and eggs, contain two copies of each gene. That is, all the genes we need are encoded by 23 chromosomes, but our cells contain a duplicate copy of each chromosome—or a total of 46.

DNA can be damaged in several ways. For example, energy metabolism in cells can produce toxic molecules called reactive oxygen species, a class of "free radicals." These substances can react with and modify the bases in DNA and prevent the code from being used properly. In fact, the DNA in each cell of our bodies probably sustains at least 10,000 injuries or errors each day! If DNA is like a zipper, free radicals produce stray threads or distorted teeth that can jam and break the zipper. Exposure to toxins, such as ultraviolet light or cigarette smoke, can also damage DNA. And the enzymes that make new DNA (which happens just before a cell divides) occasionally make mistakes. They can accidentally insert improper base pairs, resulting in DNA mutations. Erroneous repair of DNA damage during replication is quite common.

DNA REPAIR

Of course, DNA damage needs to be repaired. And our cells have evolved a sophisticated system of recognizing the multitude of possible chemical lesions in DNA and fixing them. To return to the analogy of DNA as a zipper, picture our cells as having tiny scavenger proteins that spend all of their time searching for and eliminating stray threads and foreign matter and broken teeth that have made their way into our DNA zippers. This process of weeding out such damage is DNA repair.

WHY IS DNA REPAIR IMPORTANT?

In both dividing and non-dividing cells, DNA is vital to their everyday functioning. The code in DNA is read by special enzymes and "translated" into the proteins that carry out all of our cellular and other bodily processes. Even small errors in DNA sequence can have serious effects. A single unrecognized and uncorrected DNA error can disable a critically needed protein and, over time, result in disease or even death.

Our cells must have the ability to repair lesions in their DNA to survive. If the DNA of dividing cells is sufficiently damaged, the DNA cannot be properly copied, and the cells cannot divide. Instead, they turn into senescent (dysfunctional and no longer dividing) cells or simply die. Alternatively, the DNA damage can be fixed and the chemical integrity of the DNA molecule restored, but due to partial infidelity of the repair mechanisms the original genetic code can be altered, resulting in a mutation. Mutations are permanent changes in the genetic code, which, unlike DNA damage, cannot be recognized and fixed by the DNA repair mechanisms.

The genes in the nuclei of our cells are not the only sources of DNA in our cells. Cells also contain many tiny organelles called mitochondria. Mitochondria act as

powerhouses for our cells, transforming oxygen and other fuels into the energy we need to live. Mitochondria possess their own DNA, and they use it to produce the proteins that carry out energy production. Because mitochondria use oxygen in energy production, their DNA is surrounded by free radicals (the toxic byproducts of energy production), and this greatly increases the amount of damage their DNA can sustain. For many years, scientists believed that mitochondrial DNA had no effective repair mechanisms. More recent research has shown that some mitochondrial DNA repair systems do in fact exist, but they are much less effective than those in the nuclei. This may be a reason why the mutation rate in mitochondrial DNA is much higher than that of nuclear DNA.

HOW DOES DNA REPAIR WORK?

For any creature to survive, it must be able to reproduce its DNA faithfully. For example, a substantial number of our genes are devoted solely to repair of DNA damage. Researchers have outlined the steps involved in repairing damaged or mismatched bases in DNA within human cells. They are:

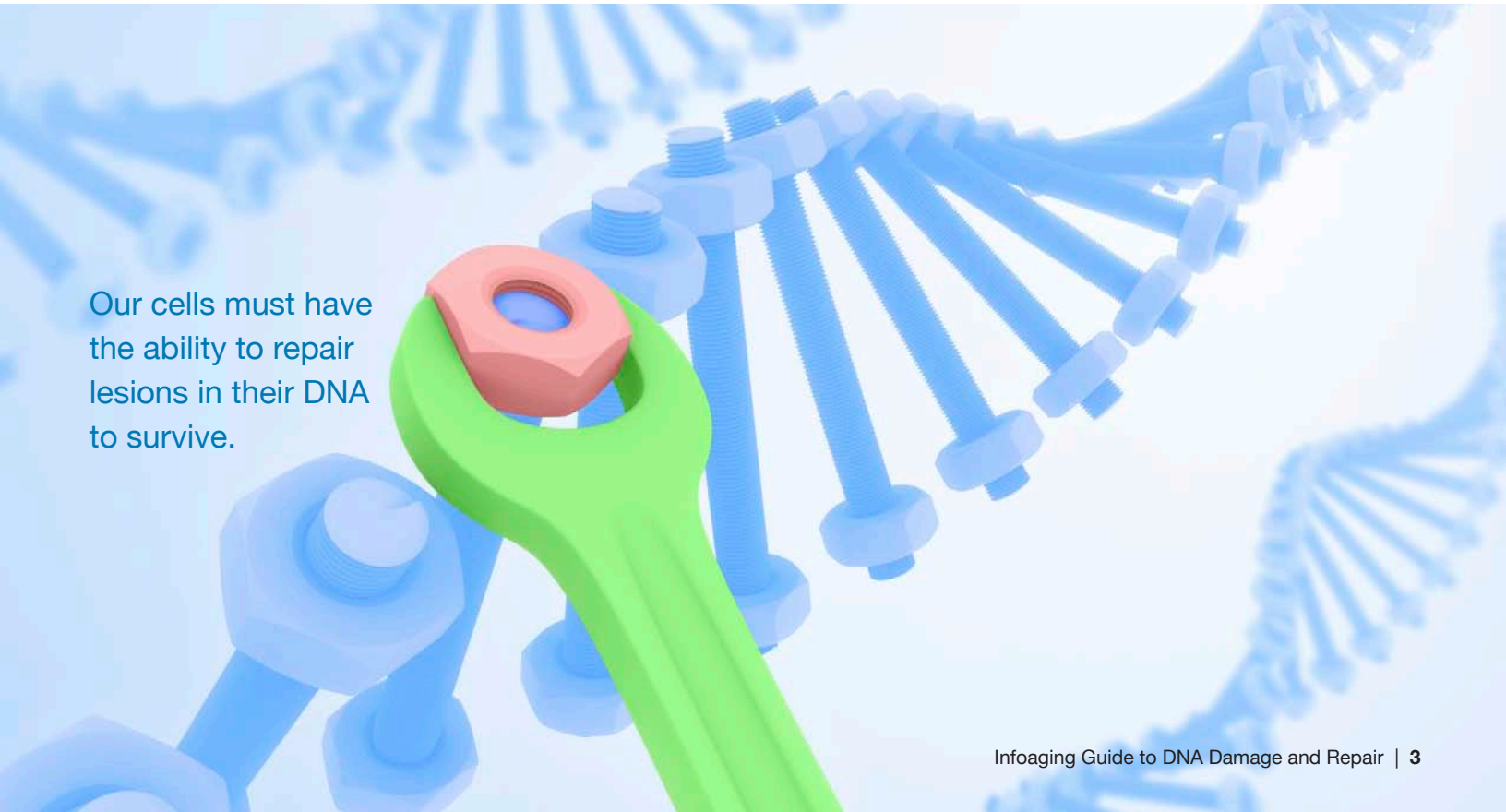
- Recognition of the damage
- Uncoiling the segment of DNA with the damage
- Making a snip in the DNA on either side of the damaged piece
- Removal of the damaged segment
- Recreation of the tiny piece of DNA that was damaged using the undamaged DNA strand for instructions to recreate the proper nucleotide sequence
- "Gluing" the new, correct bit of DNA back into the whole strand

Actively dividing cells, which are more vulnerable to errors during repair, have "proofreading" and mismatch repair systems to ensure that no errors have been made that would result in mutations. Nevertheless, errors do occasionally occur and cannot be avoided.

SINGLE STRAND AND DOUBLE STRAND BREAKS

Occasionally, the DNA strand is actually broken. This can be caused by chemicals or free radicals, and particularly by certain forms of radiation. If the break occurs in one of the two strands, that is called a DNA single-strand break. These can be repaired by processes similar to those that repair damaged or mismatched bases; the broken pieces are eventually "glued" back together.

When both strands are broken, the result is called a DNA double strand break. These are the most potentially catastrophic types of DNA damage. Imagine the structural damage when both vertical shafts of a ladder are broken. Our cells, however, can still repair this damage through an intricate,



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multi-stage process. Each step requires a different DNA repair protein, and successful repair requires that all of these proteins work correctly, in the proper order. It is a complex, almost miraculous piece of work. However, sometimes when there are multiple double-strand breaks in a cell, the wrong ends are annealed, resulting in the type of chromosomal alterations often found in cancer. Scientists have also recently discovered that certain sequences of junk DNA called retrotransposons can jump into the breach of a DNA double strand break, knitting it together again.

HOW DO DNA DAMAGE AND REPAIR RELATE TO AGING?

Some scientists believe that the accumulation of uncorrected DNA damage over years is a major cause of aging. They cite the following observations:

- Animals with the fastest rates of DNA repair generally have the longest life spans.
- Animals with the highest rates of oxidative damage by free radicals (and specifically, with oxidative damage to DNA) generally have the shortest life spans.
- In lower life forms subject to oxidative damage, antioxidant supplements, which can correct and prevent DNA damage when it occurs naturally, do increase life span. This has been shown in worms, insects, and rats.
- Exposure to external causes of DNA damage (ultraviolet light, tobacco) decreases life span.
- Humans who have genetic diseases resulting in greater spontaneous DNA damage or inefficient DNA repair often show signs of premature aging.

Several different types of cells taken from elderly subjects show evidence that DNA repair declines and DNA damage accumulates with age. Elderly patients' blood and skin cells have less capacity to repair themselves than those from young adults. Indeed, one study that looked in white blood cells found DNA damage in two to four percent of the cells from young adults, but six times more often in cells from the elderly. These aging white blood cells with their higher level of DNA damage may explain some of the decline in immune function associated with aging.

DNA damage also contributes to the development of age-related diseases, such as heart disease, lung cancer, and atherosclerosis. DNA damage from cigarette smoke is a primary culprit in each of those diseases. In addition, oxidative damage is also linked to Alzheimer's disease and macular degeneration.

WHAT CAUSES DNA DAMAGE?

Causes of DNA damage fall into two broad categories: natural cell processes and external causes.

Natural cell processes
The creation of energy in a cell utilizes oxygen. In addition to energy, that process produces toxic byproducts called reactive oxygen species. These are a class of free radicals, which can damage DNA as well as cellular proteins and fats.

External causes
Ultraviolet light has been recognized as a cause of DNA damage for nearly 25 years. X-rays can break the strands of DNA in cell nuclei. Toxins like benzo[a]pyrene, medications like those used in chemotherapy, and that most deadly poison, cigarette smoke, all cause DNA damage.

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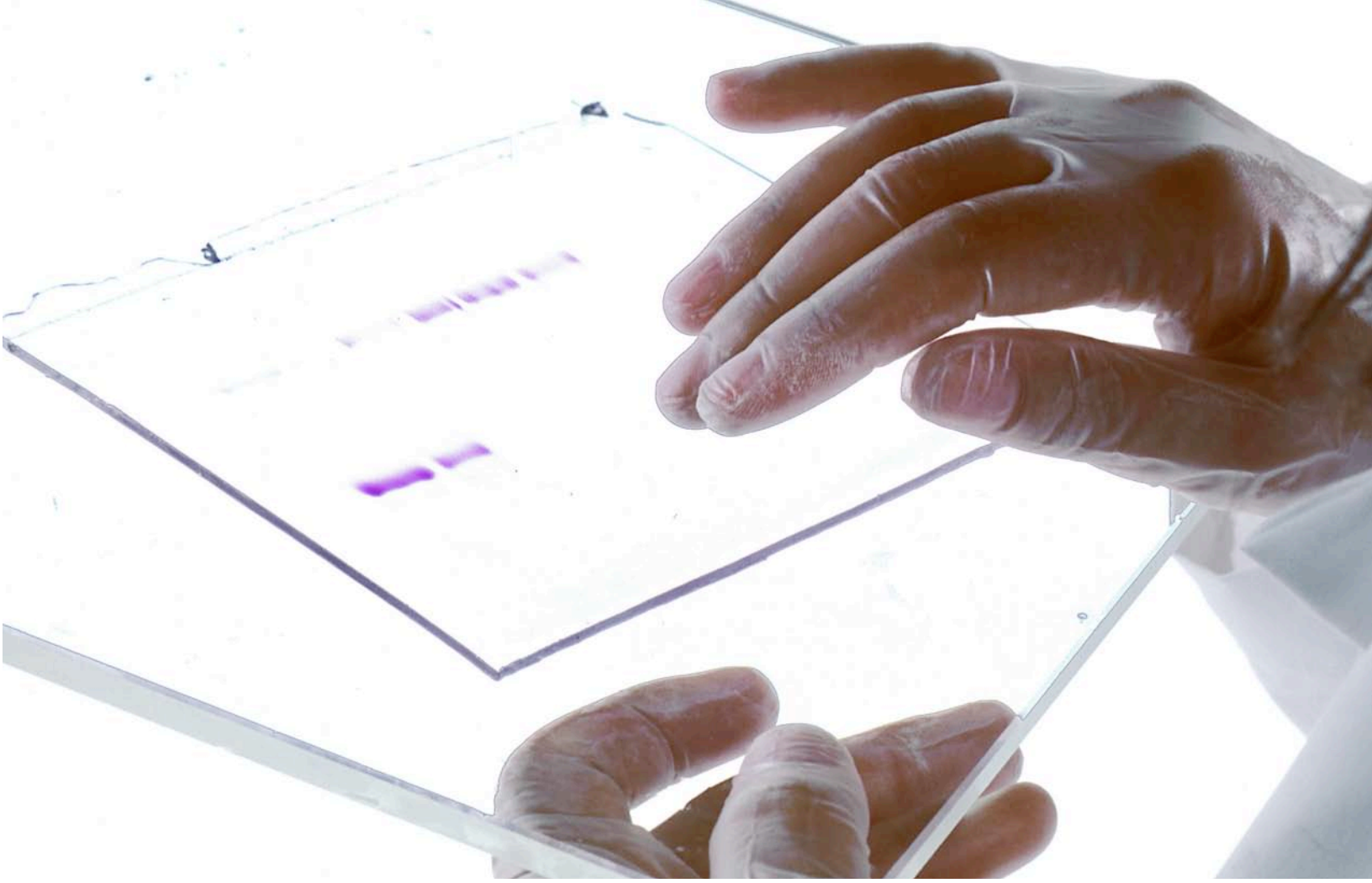

Researchers are exploring why some people age more successfully than others. They are looking at the genes that govern DNA repair and asking if there are some versions of those genes that offer greater benefits than others. Photo courtesy National Cancer Institute.

HOW DO DNA DAMAGE AND REPAIR RELATE TO CANCER?

Most normal somatic (body) cells in humans have limited reproductive life spans. Most somatic cells that continue dividing after birth can only reproduce so many times. When cells can no longer divide, they become dysfunctional, or senescent. Some senescent cells die, whereas others may accumulate in aged tissues. Cells that don't divide after birth, such as brain and heart cells, eventually senesce and die as well.

DNA damage followed by ineffective repair has been linked to several types of cancer. Cancer cells have acquired mutations in their DNA that permit them to bypass the normal limits of cell division. They become immortal and reproduce indefinitely as tumor cells. Cancer-causing DNA mutations also include the loss of genes that act as tumor suppressors and the activation of oncogenes, which promote cancer.

The abnormal insertion of methyl groups into DNA at the regulatory portion of certain genes has been noted in many cancers, particularly those that arise in the blood cells. This observation has prompted researchers to try to design chemotherapeutic drugs that might reverse or prevent those abnormal methyl group insertions. One such drug is decitabine, and it has indeed been shown to have efficacy in certain blood cancers.

Inherited cancers

Some cancers run in families. Some of these inherited cancers can be traced to a DNA error called base-pair mismatch, in which the subunits of DNA get lined up improperly. Normal cells have efficient mismatch repair systems; a few of us inherit defective genes for mismatch repair, and thus are prone to certain cancers. This is one of

nature's ironies: an inherited type of DNA damage paves the way for later acquired DNA mutation and cancer.

Sometimes people inherit a susceptibility to damage by certain environmental agents. For example, albinos have inherited an absence of skin and hair pigments. They are unprotected from sunlight and ultraviolet light, which cause DNA damage.

Some cancer may be the result of inadequate DNA repair. Certain genetic diseases that feature diminished DNA repair capacity are associated with high rates of cancer. For example, patients with xeroderma pigmentosum, an inherited disorder resulting in reduced DNA repair, have a predisposition to skin cancer.

Accumulating evidence also suggests that some breast cancers may be due to an inherited insufficiency in DNA repair. About half of all inherited cases of breast cancer are linked to a mutation in the gene BRCA1. Scientists exploring the role of the non-mutant form of BRCA1 have found the protein seems to play an important role in triggering repair of broken strands of DNA.

Externally caused cancers
Not all cancers arise from a DNA mutation that we have at birth. Most cancers arise from the accumulated mutations in our somatic cells caused by years of exposure to external toxins. One of the most deadly of these toxins is cigarette smoke. Cigarette smoke has been extensively analyzed and found to contain hundreds of potential cancer-causing substances. Many of these toxins damage DNA by attacking the bases, creating DNA adducts (large, disruptive molecules that muck up DNA). Interestingly, cells in the lungs have been found to be less efficient at repairing and removing DNA adducts than other cells in the body. This allows the number of lung cells with DNA adducts to rise, which may eventually lead to cancer.

HOW ARE SCIENTISTS STUDYING DNA DAMAGE AND REPAIR?

With the recent decoding of the human genome, research into human DNA damage and repair continues at the forefront of science. Among the areas that intrigue scientists is in-depth research into the premature aging syndromes such as Werner syndrome. Scientists are learning how the genes that relate to this and other syndromes like it act, realizing that understanding the genetics of premature aging may also lead to understanding the genetics of normal aging.

Researchers are also exploring why some people age more successfully or later than others. They are looking at the genes that govern DNA repair and asking if there are some versions of those genes that offer greater benefits than others. This phenomenon, called polymorphism, refers to the fact that genes come in different variants. Think of the genes for eye color—they appear on the same spot on each of our chromosomes, but some of us inherit a gene for blue eyes at that spot, others for brown. Similarly, some of us probably inherit genes that promote accurate and successful DNA repair, while others inherit less robust DNA repair systems.

As scientists develop a greater understanding of the processes of DNA damage and repair, they will also pursue research into controlling those processes. An exciting area of research will be the development of treatments that can reduce the rate of DNA damage and other treatments that can improve the efficiency and accuracy of DNA repair mechanisms.

American Federation for Aging Research (AFAR)
55 West 39th Street, 16th Floor
New York, NY 10018

Phone: (212) 703-9977
Toll-free: (888) 582-2327
Fax: (212) 997-0330
Email: info@afar.org

Websites:
www.afar.org
www.afar.org/infoaging

Facebook and Twitter:
AFARorg